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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,737	09/19/2001	Rajiv Chopra	W2025-701110/AM100448	9455

76595 7590 10/30/2008

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

NOTIFICATION DATE	DELIVERY MODE
10/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/955,737	CHOPRA ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16,18-24,26,27,33-35 and 41-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24,26,27,33,35,42 and 43* is/are rejected.

7)☒ Claim(s) *12-16,18,19,34 and 41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 12-16, 18-24, 26-27, 33-35, and 41-43 are pending in the application.

[2] Applicant's amendment to the claims, filed on 7/7/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. By the instant claim amendment claims 12-16, 18-24, 26-27, 33-35, and 41-43 have been amended and claims 36-40 have been canceled.

[3] Applicant's arguments filed on 7/7/08 in response to the Office action mailed on 1/7/08 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[5] Claims 12, 20, and 43 and claims dependent therefrom are objected to in the recitation of "identifying the amino acid residues…in order to generate a three-dimensional model…" in steps (b) of claims 12 and 20 and step (c) of claim 43, followed by a step of "employing said three-dimensional model from step (b). Although the examiner has interpreted the claims as requiring generating a 3-D model, in order to substantially improve claim form, it is suggested that the claims be amended to recite an

active step of generating a 3-D model rather than merely reciting the limitation "in order to generate a three-dimensional model..." as an intended use of the "identifying" step.

[6] Claims 41-42 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 41-42 are product-by-process claims, reciting how the structural coordinates of Figures 1A-1EEE were obtained, *i.e.,* x-ray crystallography. However, it is noted that the recited product-by-process limitation does not appear to further limit the recited structural coordinates and as such fails to further limit the methods of claims 12 and 20, respectively.

[7] Claim 43 and claims dependent therefrom are objected to in the recitation of “generating a three-dimensional representation from the three-dimensional coordinates…” in step (b) and “identifying the amino acid residues forming the APP-binding site…” in step (c) because the 3-D representation formed in step (b) is not required to have the 3-D coordinates of the complex of step (a), and thus is not required to have the recited BACE amino acids. In order to substantially improve claim form, it is suggested that step (b) be amended to recite, *e.g.,* "generating a three-dimensional representation of the complex..."

Claim Rejections - 35 USC § 112, Second Paragraph

[8] Claims 20-24, 26-27, and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 (claims 21-24, 26-27, and 42 dependent therefrom) is confusing in that step (d) recites "synthesizing said candidate agent", which is followed by step (e) reciting "contacting said candidate agent with the three-dimensional model..." The term "synthesizing" would typically be interpreted by a skilled artisan as meaning physically preparing the candidate agent by a chemical synthetic process. However, the three-dimensional model of step (e) of claim 20 is interpreted as being a computer-generated representation and it is unclear as to how one contacts a physical agent with a computer-generated "three-dimensional model". It is suggested that applicant clarify the meaning of the claim.

In the interest of advancing prosecution, since the claim requires the synthesized candidate agent to be contacted with the 3-D model in step (e) of claim 20, the examiner has interpreted the term "synthesizing" in step (d) as encompassing preparing the recited candidate agent by an *in silico* process.

Claim Rejections - 35 USC § 101

[9] The non-statutory subject matter rejection of claims 20-23 under 35 U.S.C. 101 is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 12 beginning at p. 5 of

the 1/7/08 Office action. Claim 42 has been included in the rejection in view of the instant claim amendment. Thus, claims 20-23 and 42 are rejected.

RESPONSE TO ARGUMENT: At p. 11 of the instant remarks, applicant argues the rejection is obviated by amendment to "require at least one concrete active step".

Applicant's argument is not found persuasive. As noted above, the examiner has interpreted step (d) of claim 20 as encompassing an *in silico* synthesis step since the "contacting" step (e) recites contacting the candidate agent with the 3-D model. These steps can be performed solely by a computer without requiring a transformation of the data.

Also, applicant may argue the step of "contacting…said candidate agent with BACE to determine the ability…whereby the detection of the ability...identifies said candidate agent" in claim 20 step (e) produces a "useful, concrete and tangible result" in providing a selection step that would narrow the set of candidate agents to a subset that are more likely to bind or interact with BACE. However, it is noted the recitation of "to determine the ability…" in the above noted phrase has been interpreted as an intended use of the "contacting" active step and not an active method step itself. Put another way, the "contacting" step does not require actively determining the ability of the candidate agent to interact or bind. Moreover, the recitation of "whereby the detection of the ability…" limitation does not require an active selection of those candidate agents that are more likely to bind or interact from those that are not.

Further, applicant may argue that claim 42 requires the structural coordinates to have been obtained by x-ray crystallography and thus requires at least one *ex silico*

active step. However, it is noted that claim 42 has been interpreted as a product-by-process claim, describing the method how the structural coordinates were obtained, but not requiring active steps in the method to obtain the coordinates.

Thus, because the claims encompass method steps that can occur solely within a computer and do not require a transformation of the data or a "useful, concrete and tangible result", *e.g.,* an active selection step, the claims are considered to be non-statutory subject matter.

Claim Rejections - 35 USC § 112, First Paragraph

[10] The written description rejection of claims 33, 35, and 43 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 13 beginning at p. 6 of the Office action mailed on 1/7/08.

RESPONSE TO ARGUMENT: Beginning at p. 11, bottom of the instant remarks, applicant argues the issues of unpredictability associated with protein crystallography "are not relevant to the claims" because the claims "specify the three-dimensional structural coordinates of the complex…and the particular crystal space group and unit cell parameters".

Applicant's argument is not found persuasive. Claim 43 requires an active step of obtaining structural coordinates by "subjecting a co-crystal to X-ray diffraction...the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-477 of SEQ ID NO:1...the APP inhibitor in the complex comprises the

amino acid sequence SEVNStaVAEF...said co-crystal has space group symmetry I222, and has unit cell parameters a=86.627, b=130.861 Å, and c=130.729 Å and α=β=γ=90°". Regarding the BACE peptide, the transitional phrase "consists essentially of" is used in reciting the sequence of the BACE peptide and according to applicant, "It is noted for the record that the human BACE peptide amino acid sequence recited in the claims…may contain additional non-BACE elements that do not materially affect the basic and novel characteristics of the claims" (instant remarks at p. 12, middle). According to MPEP 2111.03, "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to 'comprising.'" Here, there is no "clear indication in the specification or claims" of what applicant intends as being the basic and novel characteristics of the BACE peptide and thus the transitional phrase "consists essentially of" has been interpreted as equivalent to "comprising". In view of this interpretation, the BACE peptide of the co-crystal *comprises* amino acids 58-447 of SEQ ID NO:1 and the APP inhibitor *comprises* SEQ ID NO:3.

Although applicant asserts the issues of unpredictability do not apply here, the examiner disagrees. In this case, there is a high level of unpredictability in altering the amino acid sequence of a polypeptide or inhibitor peptide, *e.g.,* by addition of amino acids at the N- and/or C-terminus, with an expectation that the resulting co-crystal with achieve a desired space group and unit cell dimensions. As noted by McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) at p. 13, column 2) and undisputed by applicant, "Table 2 lists physical, chemical and biological variables that may influence to a greater

of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*" (emphasis added). Thus, as acknowledged by McPherson, even minor alterations to a polypeptide may influence protein crystallization and thus it is highly unpredictable as to whether or not BACE and/or APP inhibitor as set forth in the claims can be crystallized at all, much less to achieve the recited space group and unit cell dimensions. This is evidenced by the reference of Tang et al. (US Patent 6,545,127; cited in the 10/29/03 IDS), which teaches a crystal of human BACE, which appears to encompass the recited range of amino acids 58-447 of SEQ ID NO:1 herein, yet, as acknowledged by applicant (10/3/07 remarks at p. 25, middle), forms a crystal with a distinct space group and unit cell dimensions from those recited in the claim. Here, the specification discloses only a single BACE polypeptide and a single APP inhibitor that will achieve the space group symmetry I222 and vector lengths a=86.627, b=130.861 Å, and c=130.729 Å and $\alpha=\beta=\gamma=90^{o}$, *i.e.,* the BACE peptide of amino acids 58-447 of SEQ ID NO:1 and the peptide SEQ ID NO:3. Put another way, neither the specification nor the prior art discloses a relationship between the structures of peptides comprising SEQ ID NO:1 and 3 and the ability to form a crystal with the space group symmetry I222 and vector lengths a=86.627, b=130.861 Å, and c=130.729 Å and $\alpha=\beta=\gamma=90^{o}$. Other than the single respective species of BACE and APP inhibitor peptides, the specification fails to

disclose any other peptides comprising SEQ ID NO:1 and/or 3 that will co-crystallize to achieve the recited space group and unit cell parameters.

For at least the reasons of record and those presented above, it is the examiner's position that the specification fails to adequately describe the claimed invention.

[11] The scope of enablement rejection of claims 33, 35, and 43 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 14 beginning at p. 12 of the Office action mailed on 1/7/08.

RESPONSE TO ARGUMENT: Beginning at p. 11, bottom of the instant remarks, applicant argues the rejection is obviated in-part by amending the claims to recite the transitional phrase "consisting essentially of" with respect to the BACE and APP inhibitor peptides and further amended such that the claims "are not intended to require *de novo* crystallization…without the benefit of the solved structure".

Applicant's argument is not found persuasive. As noted above, claim 43 requires an active step of obtaining structural coordinates by "subjecting a co-crystal to X-ray diffraction...the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-477 of SEQ ID NO:1...the APP inhibitor in the complex comprises the amino acid sequence SEVNStaVAEF...said co-crystal has space group symmetry I222, and has unit cell parameters a=86.627, b=130.861 Å, and c=130.729 Å and $\alpha=\beta=\gamma=90^{o}$". As further noted above, the transitional phrase "consists essentially of" has been interpreted as equivalent to "comprising". In view of this interpretation, the

BACE peptide of the co-crystal *comprises* amino acids 58-447 of SEQ ID NO:1 and the APP inhibitor *comprises* SEQ ID NO:3.

As noted in a prior Office action and undisputed by applicant, Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). See also the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons.

Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids" (emphasis added). Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." See the example of Tang et al. (US Patent 6,545,127; cited in the 10/29/03 IDS) above, which teaches a crystal of human BACE, which appears to encompass the recited range of amino acids 58-447 of SEQ ID NO:1 herein, yet, as acknowledged by applicant (10/3/07 remarks at p. 25, middle), forms a crystal with a distinct space group and unit cell dimensions from those recited in the claim. Thus, in view of these teachings, a skilled artisan would recognize there is a *high* level of unpredictability in making a protein crystal.

At least for the reasons of record and the reasons set forth above, the specification fails to enable the full scope of the claimed invention. The examiner has properly considered all Factors of *In re Wands,* and when the evidence is taken as a whole (MPEP 2164.05), it is the examiner's position that the specification in view of the prior art fails to enable the full scope of the claimed invention, particularly with respect to the scope of BACE peptides and APP inhibitor peptides.

Claim Rejections - 35 USC § 102/103

[12] The rejection of claims 20-21, 23-24, 26-27, 34, and 36 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tang et al. (US Patent 6,545,127; "Tang") is withdrawn in view of the claim amendment to require the APP inhibitor peptide of the complex to comprising SEQ ID NO:3.

Claim Rejections - 35 USC § 103

[13] The rejection of claim(s) 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (*supra*) in view of In re Gulack 217 USPQ 401 (Fed. Cir. 1983) is withdrawn at least in view of the claim amendment to require identifying the recited APP binding site residues of BACE and generating a 3-D model thereof. Since the prior art does not appear to teach these limitations, the difference between the prior art and the claimed invention goes beyond the non-functional descriptive material of the structural coordinates of Figures 1A to 1EEE.

Conclusion

[14] Status of the claims:

Claims 12-16, 18-24, 26-27, 33-35, and 41-43 are pending.

Claims 20-24, 26-27, 33, 35, and 42-43 are rejected.

Claims 12-16, 18-19, 34, and 41 are objected to, but would otherwise appear to be in a condition for allowance.

No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656